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Catecholamines participate in the induction of ornithine decarboxylase gene expression in normal and hyperplastic mouse kidney

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Abstract

In the quinazoline antifolate (CB 3717)-induced hyperplastic kidney model, a remarkable increase of ornithine decarboxylase (ODC) activity was paralleled by a smaller, but highly significant augmentation of the ODC transcript level. Catecholamine depletion, evoked by reserpine, strongly impaired antifolate-induced ODC expression; the enzyme activity was almost completely abolished while the mRNA level decreased by 60%. Moreover, under conditions of a depleted catecholamine pool, kidney enlargement was significantly reduced confirming our earlier reports on the indispensability of ODC induction for renal hyperplasia (M. Manteuffel-Cymborowska et al., Biochim. Biophys. Acta, 1182 (1993) 133–141[1]). In normal mouse kidney catecholamines appeared to be inducers of ODC expression. Use of selective agonists of catecholamine receptors demonstrated the importance of dopamine D2 receptors, and to a lower extent β adrenoreceptors, in the catecholamine mediation of induction of ODC activity and of ODC mRNA levels.These increases were not abolished by an antiandrogen, casodex, suggesting that catecholamine control of ODC expression is an androgen receptor-independent process. The results obtained point to the critical role of renal catecholamines; these biogenic amines are not only involved in the regulation of ODC expression in normal kidney but are also required for the induction of ODC in hyperplastic kidney evoked by antifolate and, as shown recently (M. Manteuffel-Cymborowska et al., Biochim. Biophys. Acta, 1356 (1997) 292–298[2]), in testosterone-induced hypertrophic kidney.

Keywords: Ornithine decarboxylase gene expression; Antifolate CB 3717; Catecholamine receptor; Reserpine; (Kidney hyperplasia)

1. Introduction

Extracellular signaling substances, acting at their cell membrane or nuclear receptors, activate specific transduction pathways and elicit a genomic or non-genomic response in target cells. Recently, it has been recognized that diverse signaling pathways do not act independently but are interconnected with one another and form a complex network integrated at different levels [3–7].

Ornithine decarboxylase (ODC), the first and rate-limiting enzyme of polyamine biosynthesis, is an example of a protein regulated by various metabolic, hormonal and neuronal signals [8–13]. The spectacular induction of ODC and its role in mouse kidney undergoing hypertrophy and hyperplasia evoked by

Abbreviations: ODC, ornithine decarboxylase; CB 3717, N^{10}-propargyl-5,8-dideazafolic acid; DFMO, α-difluoromethylornithine

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the steroid sex hormone, testosterone, and agents causing renal injury, respectively, has been thoroughly studied in our laboratory [1,2,14–17]. Recently, we have documented that catecholamine depletion, evoked by reserpine, dramatically impairs the testosterone-induced increase of ODC expression in mouse kidney without affecting its hypertrophy [2]. This is in agreement with evidence that catecholamines are important for the induction of ODC activity by steroids in the liver and kidney [18–21]. Thus, both the androgen and catecholamines appear to be involved in the activation of ODC gene expression. Androgen and catecholamine signaling pathways are likely to integrate at the level of androgen receptor or transcriptional coactivator(s) [6,7,22]. Androgen receptor is a member of the superfamily of nuclear receptors acting as transcription factors activated by cognate lipophilic ligands [23–25] and/or alternatively by hydrophilic signaling substances from the cell surface [3–5].

Data about the involvement of catecholamines in the induction of ODC during renal hyperplasia are lacking. We approach this problem using our model of renal hyperplasia in which an anticancer drug, a quinazoline analogue of folic acid, N^{10}-propargyl-5,8-dideazafolic acid (CB 3717), is used as an agent to induce renal damage. This occurs due to its precipitation at physiological pH in renal tubules [1,14]. The resulting injury of tubular epithelium is followed by its regenerative hyperplasia. This is characterized by the augmentation of DNA synthesis and the increase in the activity of two key enzymes of polyamine biosynthesis, namely ODC and *S*-adenosylmethionine decarboxylase. The putrescine and spermidine content is also augmented whereas spermine level is significantly decreased [1,14].

In this paper we present in vivo data on the inhibitory effect of catecholamine depletion evoked by reserpine treatment on the CB 3717-induced increase of ODC activity and ODC mRNA level in hyperplastic kidneys. Moreover, we show that the activation of dopamine receptors and adrenoreceptors by specific agonists leads to the induction of ODC expression in the normal mouse kidney. The signaling pathway likely to be activated in the injured kidney by the administered antifolate is discussed.

2. Materials and methods

2.1. Experimental

Swiss female mice, 2.5–3 months old, were injected with a quinazoline antifolate CB 3717 (300 mg/kg) dissolved in phosphate-buffered saline (PBS) with addition of a few drops of 1 M NaOH to final pH 9–9.5 (controls received PBS only) for 24 h. Reserpine (10 mg/kg) was given 96 h or 1 h before CB 3717. The dosage (according to literature) and timing of the applied catecholamine receptor agonists (phenylephrine, [19]; isoproterenol, [19]; apomorphine, [26]; SKF 38393, [27]; quinpirole, [28]), antagonists (phenoxybenzamine, [20]; propranolol, [20]; spiroperidol, [29]; SCH 23390, [30]) and antiandrogen casodex [31] is shown in the legends of the appropriate figures and tables. All drugs were injected i.p. with the exception of casodex which was given s.c. The mice were killed by cervical dislocation, the kidneys were removed, weighed, and cut into several pieces.

2.2. Enzyme activity and Northern blot analysis

The kidney pieces were immediately homogenized in an appropriate buffer and further processed for enzyme activity determinations as previously described [16], or were frozen at −70°C and processed for ODC mRNA estimation as described [2]. The pODC 934 plasmid containing 1.4 kb mouse ODC cDNA insert was used as a probe. The protein concentration was estimated according to the method of Lowry et al. [32]. The results are expressed as means ± S.D.; the number of mice is given in parentheses. Data were statistically analyzed by the Mann–Whitney test.

2.3. Chemicals

All chemicals purchased from commercial sources were of analytical grade. Reserpine and apomorphine were obtained from Sigma, phenylephrine (as Neo-Synephrine) and isoproterenol (as Isuprel) were from Winthrop USA and France, respectively. SKF 38393, quinpirole, phenoxybenzamine, spiroperidol and SCH 23390 were from RBI, USA. Propranolol was from ICI, UK. Rediprime (Random Primer Label-

ing), Hybond-N, Hyperfilm-MP, [α-^{32}P]dCTP (110 TBq/mmol) and DL-[1-^{14}C]ornithine hydrochloride (2.15 GBq/mmol) were obtained from Amersham, UK. CB 3717 and casodex were generously provided by Zeneca Pharmaceuticals, Alderly Park, Macclesfield, Cheshire, UK.

3. Results

3.1. Effect of reserpine on antifolate-induced ODC gene expression and kidney hyperplasia

Catecholamine depletion, evoked by reserpine, dramatically impaired the CB 3717-induced increase of ODC activity characteristic for mouse kidney undergoing hyperplasia (Fig. 1). Thus, in the presence of reserpine, administered 1 h before CB 3717, the ODC activity reached less than 6% of the activity induced by the antifolate alone. Depletion of endogenous catecholamines by reserpine persisted for several days as evidenced by the weaker but still significant effect of reserpine administered 96 h prior to CB 3717 (Fig. 1).

While depletion of catecholamines prevented ODC induction by antifolate, the additional activation of catecholamine receptors did not further increase antifolate-induced ODC activity. This was shown in experiments with quinpirole (Fig. 1) and apomorphine (data not shown), dopamine receptor agonists, that induced ODC expression in normal kidney (compare Section 3.3). It appears, therefore, that renal endogenous catecholamine levels were sufficient for the maximal ODC activation in kidneys undergoing hyperplasia.

The spectacular increase of ODC activity in CB 3717-induced hyperplastic kidney was paralleled by a nearly 3-fold, highly significant augmentation of

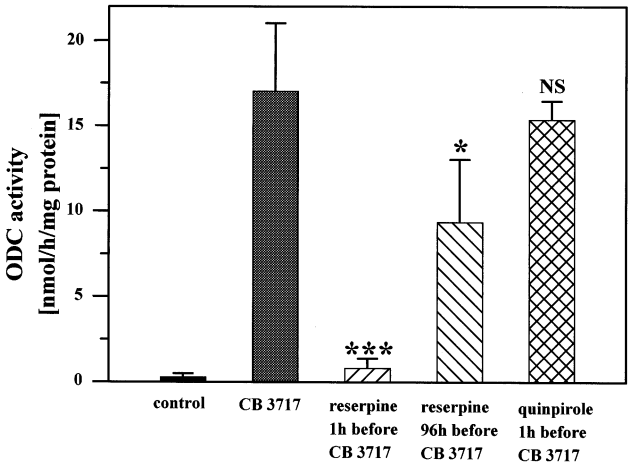

Fig. 1. The effect of reserpine or quinpirole (10 mg/kg) on CB 3717-induced ODC activity. P values vs. CB 3717-treated mice are: $*P<0.05$; $***P<0.001$; NS, not significant.

ODC mRNA levels; the result of a representative experiment is shown in Fig. 2A. Catecholamine depletion, produced by reserpine administered 1 h before CB 3717, lowered the ODC transcript level by at least 60% (Fig. 2B). The increase of ODC mRNA evoked by antifolate alone, and decrease by coadministered reserpine and antifolate, although very significant was, however, less pronounced than the changes of ODC activity under the same conditions.

The CB 3717-induced enlargement of the kidneys connected with regenerative hyperplasia of the injured renal tubular epithelium was also affected by catecholamine depletion (Table 1). Thus, reserpine given 1 h (but not 96 h) before CB 3717 prevented, to some extent, drug-induced kidney enlargement, the effect being highly significant. This response of kidney hyperplasia was in contrast to testosterone-induced kidney hypertrophy which was insensitive to reserpine treatment [2].

Table 1
Effect of reserpine on kidney enlargement in CB 3717-treated mice

Treatment	Relative kidney weight (% of the body weight)	P value
Control	1.11 ± 0.09 (16)	
CB 3717	2.03 ± 0.17 (13)	–
Reserpine 1 h before CB 3717	1.59 ± 0.19 (12)	< 0.0001
Reserpine 96 h before CB 3717	1.96 ± 0.29 (12)	NS

P value was calculated vs. CB 3717-treated mice; NS, not significant.

Table 2
Effect of α, β, D1 and D2 receptor antagonists on CB 3717-induced ODC activity

Conditions	ODC activity, %	*P* value
CB 3717	100.0 ± 16.61 (13)	–
Phenoxybenzamine (α)+CB 3717	124.9 ± 24.0 (6)	< 0.05
Propranolol (β)+CB 3717	111.7 ± 21.7 (6)	NS
SCH 23390 (D1)+CB 3717	100.1 ± 26.0 (7)	NS
Spiroperidol (D2)+CB 3717	138.7 ± 20.6 (14)	< 0.001
SCH 23390 (D1)+spiroperidol (D2)+CB 3717	95.6 ± 13.9 (5)	NS

Phenoxybenzamine (10 mg/kg) was injected twice: 1 h before and 11 h after CB 3717 (according to [20]). Propranolol (20 mg/kg) and spiroperidol (1 mg/kg) were given 1 h before CB 3717. SCH 23390 (1 mg/kg) when administered alone was injected 24 h and 1 h before CB 3717. SCH 23390 (1 mg/kg) was coadministered with spiroperidol (1 mg/kg) and injected 1 h before CB 3717.
P value was calculated vs. CB 3717-treated mice; NS, not significant.

3.2. *Attempts to identify catecholamine receptor(s) involved in ODC induction in antifolate-evoked hyperplastic kidney*

The results obtained with reserpine, which evokes catecholamine depletion, demonstrated the importance of these biogenic amines for ODC induction. Several α, β and D receptor antagonists were used to study the type of catecholamine receptor(s) that could mediate the response of renal ODC to the antifolate. None of the applied antagonists, exerted a significant decrease on the ODC activity induced by CB 3717 (Table 2). Similar, non-significant effects were observed when D1 and D2 receptor antagonists were given simultaneously (Table 2), or a 10-times higher amount of D1 receptor antagonist was applied (data not shown). It is to be noted that some of the antagonists exerted slightly agonistic effects in accordance with two previous reports [20,33]. The obtained results did not allow us, at present, to identify which catecholamine receptors are involved in CB 3717-induced ODC expression. It appears that other experimental schedules should be applied to solve this problem.

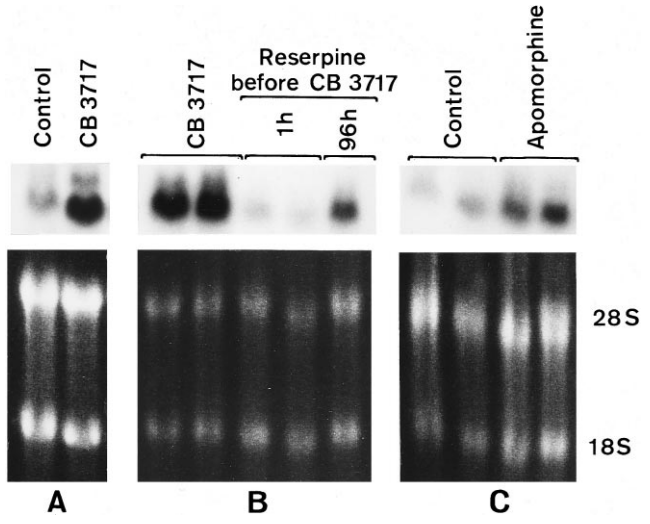

Fig. 2. The effect of CB 3717 (A), reserpine plus CB 3717 (B) and apomorphine (C) on renal ODC mRNA level as demonstrated by Northern blot analysis. 18S and 28S rRNA ethidium bromide-stained bands indicating the amount of RNA blotted onto the filter are shown below. Each lane represents RNA from an individual mouse. Mean ODC mRNA relative values ± S.D. (the number of mice is given in parentheses) and *P* values are as follows: CB 3717 (vs. control) 2.75 ± 1.34 (11), $P < 0.0001$; (B) reserpine 1 h before CB 3717 (vs. CB 3717) 0.39 ± 0.26 (8), $P < 0.001$; (C) apomorphine (vs. control) 1.79 ± 0.48 (6), $P < 0.05$.

3.3. *Effect of catecholamine receptor agonists on ODC expression in normal kidney*

To evaluate the role of catecholamines in ODC expression in normal kidney, the effect of several agonists of adrenergic and dopaminergic receptors was examined. (Fig. 3). The low renal ODC activity was not elevated by phenylephrine, an α_1 adrenoreceptor agonist, while isoproterenol, which stimulates β adrenoreceptors, caused a significant, 1.7-fold increase of ODC activity. Apomorphine, acting mainly as an agonist of D2 but also of D1 receptors, appeared even more effective as an ODC inducer. Thus, stimulation of dopamine receptors by apomorphine resulted in pronounced increase of ODC activity (Fig. 3) and lower but significant rise in ODC transcript level (Fig. 2C). In experiments with the use of

selective D1 and D2 receptor agonists, SKF 38393 and quinpirole, respectively, it appeared that only quinpirole significantly induced ODC activity while SKF 38393 was without effect (Fig. 3). These results suggest that the D2, but not the D1, receptors are implicated in ODC induction.

Transcriptional modulation of a target gene by steroid hormones, androgens included, is mediated by their nuclear receptors [23]. These ligand-dependent transcription factors can sometimes be alternatively activated by hydrophilic signaling substances, among them by catecholamines, acting via their plasma membrane receptors [4]. Thus, it could not be excluded that in mouse kidney, an androgen-responsive organ, the induction of ODC (testosterone target gene) by catecholamines is mediated by an androgen receptor. To verify this possibility an antiandrogen, casodex, that dramatically impaired the testosterone-induced ODC activity (to $12.8 \pm 6.3\%$, $n = 7$, $P < 0.01$) was applied. In contrast, this androgen receptor antagonist, when given before quinpirole (Fig. 4) or apomorphine did not prevent ODC induction, its effect being non-significant. Thus, catecholamine control of ODC expression in normal kidney appears to be an androgen receptor-independent process.

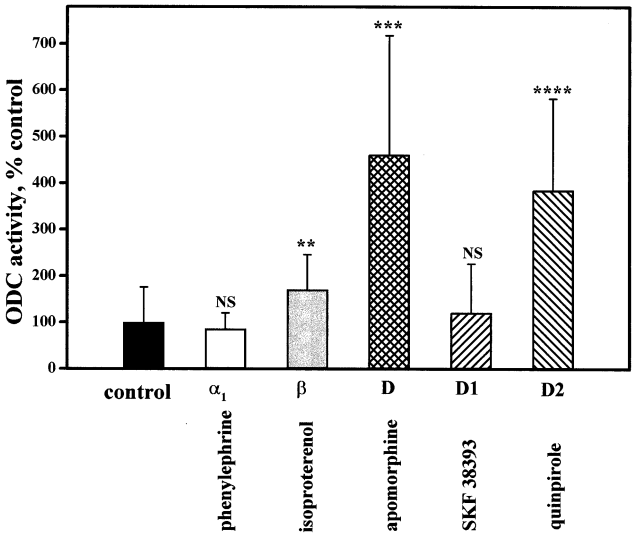

Fig. 3. Catecholamine receptor agonists as inducers of ODC activity in normal mouse kidneys. Phenylephrine (2.5 mg/kg) and isoproterenol (1 mg/kg) were injected for 4 h; apomorphine (10 mg/kg) for 1 h; SKF 38393 (10 mg/kg) and quinpirole (10 mg/kg) for 2 h. P values vs. control are: $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$; NS, not significant.

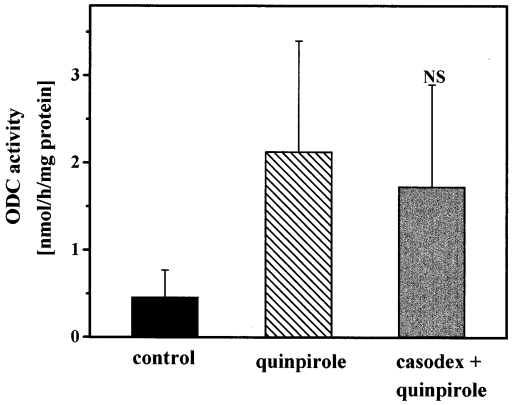

Fig. 4. The effect of antiandrogen casodex on quinpirole-induced renal ODC activity. Casodex (40 mg/kg) was injected twice: 22 h and 1 h before quinpirole (10 mg/kg) which was given to the mice for 2 h. P value was calculated vs. quinpirole-treated mice; NS, not significant.

4. Discussion

In the present study two main problems were addressed. The first dealt with the participation of catecholamines in antifolate-induced renal ODC expression and kidney hyperplasia. The second was connected with the action of catecholamines as ODC inducers in normal kidney.

Firstly, we showed that catecholamine depletion produced by pretreatment of mice with reserpine prior to antifolate administration drastically lowered the ODC activity and ODC transcript level and also prevented, to a significant extent, drug-induced kidney hyperplasia. Thus, catecholamine- and antifolate-activated pathways, similarly to previously documented androgen and catecholamine cross-talk in hypertrophic kidney [2], seem to interconnect with one another and are both involved in the activation of renal ODC expression. However, an additional activation of dopamine receptors by administered quinpirole or apomorphine did not further increase the antifolate-induced ODC activity. It seems, therefore, that the endogenous dopamine pool is sufficient to maximally induce ODC expression in hyperplastic kidneys. The identity of the catecholamine receptor involved in CB 3717-induced ODC expression is unclear because of a lack of a significant inhibitory effect of the applied catecholamine receptor antagonists at the level of this induction. One can speculate that under the applied experimental conditions (dos-

age and timing according to literature), antagonists were unable to displace endogenous catecholamines from their receptors and were therefore ineffective.

Hyperplastic and hypertrophic renal growth and the role of ODC and polyamines in these processes have been thoroughly studied in this laboratory [1,2,14–17,34]. The significant decrease of antifolate-induced renal hyperplasia concomitant with a dramatic fall of ODC expression in catecholamine-depleted mice (this paper) confirms our previous data on the sensitivity of renal hyperplastic growth to ODC inhibition evoked by DFMO [1].The ODC dependence of hyperplastic renal growth is in contrast to hypertrophic growth independence of androgen-induced ODC [1,2].

The signal transduction pathway activated in the mouse kidney by CB 3717 treatment, which in consequence leads to activation of ODC gene expression, has not been investigated in the present study. We hypothesize that an antifolate-evoked injury of epithelial cells in renal proximal tubules may induce proteolytic activation or increased expression of hepatocyte growth factor/scatter factor (HGF/SF), a potent pleiotropic cytokine playing major roles in development, regeneration and carcinogenesis [35]. HGF, among others, functions as a renotropic factor for kidney regeneration following acute renal injuries [36,37]. Our supposition is strengthened by recent data which document the increased expression of HGF and/or its membrane receptor in renal hyperplasia, acute renal injury evoked by $HgCl_2$ treatment and several different models of renal hypertrophy [36–38]. Recently, in in vitro studies, the induced expression of ODC in HGF-treated normal and neoplastic hepatocytes has been documented [39,40]. Therefore, it is highly probable that HGF may also trigger signaling pathway leading to induction of ODC in vivo in antifolate-induced hyperplastic kidney. This is at present under investigation.

Secondly, using several specific agonists of adrenergic and dopamine receptors we documented the ability of catecholamines to induce the ODC activity in normal female mouse kidney. We showed that the activation of dopamine receptors, in particular of the D2 type, and to a lesser extent of β adrenoreceptors stimulated the ODC activity severalfold concomitant with a lower, but significant increase, in ODC mRNA level. A higher induction degree of the ODC activity than its transcript level by catecholamines (and also by CB 3717) may result from an increased intracellular stability of induced ODC protein and its catalytic efficiency due to enzyme protein phosphorylation [41]

The identification of catecholamine receptors participating in ODC induction in normal kidney is based on the results of experiments with their selective agonists. The very low basal ODC activity in female mouse kidney, together with the relatively low catecholamine-evoked ODC induction and high mouse to mouse variations, made it difficult to use the appropriate antagonists. In mouse kidney mainly dopamine and to a smaller extent β receptors are involved in the induction of ODC expression (this paper). This is in contrast to adrenergic, but not dopaminic, control of ODC activity (mainly through β-adrenergic receptors linked to the adenylate cyclase system) documented in several cells and tissues [42–46]. These results point to catecholamine receptor tissue specificity in the regulation of ODC expression and a critical role of dopamine in kidneys.

In the rodent kidney, dopamine is an abundant neurotransmitter being either of neuronal origin or biosynthesized intrarenally mainly in apical poles of proximal tubular cells [47,48]. In this organ, dopamine exerts a variety of physiological actions due to activation of two main types of receptors, D1 and D2 [49]. In our studies we show that D2 receptors, and to a smaller extent β adrenoreceptors, mediate the catecholamine activating effect on ODC gene expression in normal kidneys. In this context it is noteworthy that D2 receptors colocalize in renal proximal tubules with ODC gene transcript [50,51]. The stimulation of D2 receptors coupled to many distinct signaling pathways results, among others, in the inhibition of adenylate cyclase activity and in an increase in intracellular calcium levels (via phospholipase C activation). β receptors, in contrast to D2 receptors, mediate the activation of adenylate cyclase and the opening of plasma membrane calcium channels. It is to be noted, therefore, that, while D2 and β receptor activation differentially affects the cAMP generating system, in both cases it results in calcium level increases. In this context a suggestion for the calcium mediation of catecholamine-induced processes involved in ODC gene expression in regenerating liver [52] appears to be significant.

Recently it has been established that some steroid receptors can be alternatively activated in the absence of their lipophilic ligands by a variety of extracellular signals, catecholamines included [3–5,25]. In rat hypothalamus dopamine acting through its D1 receptors was shown to activate the progesterone receptor in a ligand-independent manner and thus regulate gene expression [53]. However, in mouse kidney, an androgen responsive organ, the catecholamine-evoked induction of ODC expression, mediated mainly by D2 receptors, appears to be insensitive to an antiandrogen - casodex, suggesting that it occurs via an androgen receptor-independent pathway. Whether this catecholamine-mediated pathway depends on a coactivator and integrator CBP (CREB-binding protein), an important point of convergence for many signaling pathways [6,7,22], remains to be shown. It should also be considered that catecholamine induction of ODC gene expression may be secondary and connected with the transcriptional activation of catecholamine-dependent regulatory protein, which in turn affects ODC expression.

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References

[1] M. Manteuffel-Cymborowska, W. Chmurzyńska, B. Grzelakowska-Sztabert, Polyamines in testosterone-induced hypertrophic and antifolate-induced hyperplastic mouse kidney. Differential effect of α-difluoromethylornithine, Biochim. Biophys. Acta 1182 (1993) 133–141.

[2] M. Manteuffel-Cymborowska, M. Pęska, W. Chmurzyńska, B. Grzelakowska-Sztabert, Catecholamines are required for androgen-induced ODC expression but not for hypertrophy of mouse kidney, Biochim. Biophys. Acta 1356 (1997) 292–298.

[3] D.M. Ignar-Trowbridge, K.G. Nelson, M.C. Bidwell, S.W. Curtis, T.F. Washburn, J.A. McLachlan, K.S. Korach, Coupling of dual signaling pathways: epidermal growth factor action involves the estrogen receptor, Proc. Natl. Acad. Sci. USA 89 (1992) 4658–4662.

[4] B.W. O'Malley, W.T. Schrader, S. Mani, C. Smith, N.L. Weigel, O.M. Conneely, J.H. Clark, An alternative ligand-independent pathway for activation of steroid receptors, Recent Prog. Horm. Res. 50 (1995) 333–347.

[5] S.W. Curtis, T. Washburn, C. Sewall, R. DiAugustine, J. Lindzey, J.F. Couse, K.S. Korach, Physiological coupling of growth factor and steroid receptor signaling pathways: estrogen receptor knockout mice lack estrogen-like response to epidermal growth factor, Proc. Natl. Acad. Sci. USA 93 (1996) 12626–12630.

[6] R. Janknecht, T. Hunter, A growing coactivator network, Nature 383 (1996) 22–23.

[7] P. Aarnisalo, J.J. Palvimo, O.A. Jänne, CREB-binding protein in androgen receptor-mediated signaling, Proc. Natl. Acad. Sci. USA 95 (1998) 2122–2127.

[8] O. Heby, L. Persson, Molecular genetics of polyamine synthesis in eukaryotic cells, Trends Biochem. Sci. 15 (1990) 153–158.

[9] R.H. Davis, Management of polyamine pools and the regulation of ornithine decarboxylase, J. Cell. Biochem. 44 (1990) 199–205.

[10] M.S. Abrahamsen, D.R. Morris, Regulation of expression of the ornithine decarboxylase gene by intracellular signal transduction pathways, in: Perspectives on Cellular Regulation: From Bacteria to Cancer, Wiley-Liss, New York, 1991, pp. 107–119.

[11] A.E. Pegg, L.M. Shantz, C.S. Coleman, Ornithine decarboxylase: structure, function and translational regulation, Biochem. Soc. Trans. 22 (1994) 846–852.

[12] G.L. Law, R.-S. Li, D.R. Morris, Transcriptional control of the ODC gene, in: R. Casero (Ed.), Polyamines: Regulation and Molecular Interaction, R.G. Landes Co., 1995, pp. 5–26.

[13] A.E. Pegg, L.M. Shantz, C.S. Coleman, Ornithine decarboxylase as a target for chemoprevention, J. Cell. Biochem. Suppl. 22 (1995) 132–138.

[14] M. Manteuffel-Cymborowska, W. Chmurzyńska, B. Grzelakowska-Sztabert, Ornithine decarboxylase induction in mouse kidney as indicator of renal damage. Differential nephrotoxic effect of anticancer antifolate drugs, Cancer Lett. 59 (1991) 237–241.

[15] M. Manteuffel-Cymborowska, W. Chmurzyńska, B. Grzelakowska-Sztabert, Tissue-specific effects of testosterone on S-adenosylmethionine formation and utilization in the mouse, Biochim. Biophys. Acta 1116 (1992) 166–172.

[16] M. Manteuffel-Cymborowska, W. Chmurzyńska, M. Pęska, B. Grzelakowska-Sztabert, Arginine and ornithine metabolizing enzymes in testosterone-induced hypertrophic mouse kidney, Int. J. Biochem. Cell Biol. 27 (1995) 287–295.

[17] M. Manteuffel-Cymborowska, W. Chmurzyńska, M. Pęska, B. Grzelakowska-Sztabert, Tumour effect on arginine/ornithine metabolic relationship in hypertrophic mouse kidney, Mol. Cell. Biochem. 168 (1997) 51–57.
[18] A. Corti, S. Astancolle, P. Davalli, Response of hepatic ornithine decarboxylase and polyamine concentration to surgical stress in the rat: evidence for a permissive effect of catecholamines on glucocorticoid action, Biochem. Biophys. Res. Commun. 129 (1985) 885–891.
[19] S. Astancolle, P. Davalli, A. Corti, Blockade of α- and β-adrenergic receptors can prevent stimulation of liver ornithine decarboxylase activity by glucocorticoid or laparotomy, Biochem. Biophys. Res. Commun. 174 (1991) 915–921.
[20] A. Cremades, A. Tovar, R. Penafiel, Catecholamines are required for testosterone induction of ornithine decarboxylase in the mouse kidney, Biochem. Int. 27 (1992) 823–830.
[21] A. Tovar, A. Penuela, A. Sanchez-Capelo, F. Monserrat, A. Cremades, R. Penafiel, Neuronal regulation of ornithine decarboxylase induced by androgens in the mouse kidney, Gen. Pharmacol. 26 (1995) 997–1001.
[22] N. Shikama, J. Lyon, N.B. La Thangue, The p300/CBP family: integrating signals with transcription factors and chromatin, Trends Cell Biol. 7 (1997) 230–236.
[23] D.J. Mangelsdorf, C. Thummel, M. Beato, P. Herrlich, G. Schütz, K. Umesono, B. Blumberg, P. Kastner, M. Mark, P. Chambon, R.M. Evans, The nuclear receptor superfamily: the second decade, Cell 83 (1995) 835–839.
[24] M. Beato, P. Herrlich, G. Schütz, Steroid hormone receptors: many actors in search of a plot, Cell 83 (1995) 851–857.
[25] N.L. Weigel, Steroid hormone receptors and their regulation by phosphorylation, Biochem. J. 319 (1996) 657–667.
[26] N.K. Dadkar, A.N. Dohadwalla, B.K. Bhattacharya, Possible role of dopamine in central effects of cocaine as measured by apomorphine gnawing test in mice, Psychopharmacology 52 (1977) 115–117.
[27] E. Ongini, M.G. Caporali, M. Massotti, Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal, Life Sci. 37 (1985) 2327–2333.
[28] A. Horita, M.A. Carino, Y. Nishimura, D1 agonist SKF 38393 antagonizes pentobarbital-induced narcosis and depression of hippocampal and cortical cholinergic activity in rats, Life Sci. 49 (1991) 595–601.
[29] J. Maj, Z. Rogoz, G. Skuza, K. Kołodziejczyk, The behavioural effects of pramipexole, a novel dopamine receptor agonist, Eur. J. Pharmacol. 324 (1997) 31–37.
[30] J. Balthazart, C. Castagna, G.F. Ball, Differential effects of D1 and D2 dopamine-receptor agonists and antagonists on appetitive and consummatory aspects of male sexual behavior in Japanese quail, Physiol. Behav. 62 (1997) 571–580.
[31] F. Paris, G.F. Weinbauer, V. Blum, E. Nieschlag, The effect of androgens and antiandrogens on the immunohistological localization of the androgen receptor in accessory reproductive glands of male rats, J. Steroid Biochem. Mol. Biol. 48 (1994) 129–137.
[32] O.H. Lowry, N.J. Rosebrough, A.L. Farr, R.J. Randall, Protein measurement with the folin phenol reagent, J. Biol. Chem. 193 (1951) 265–275.
[33] M.A. Desiderio, A. Sessa, A. Perin, Regulation of diamine oxidase expression by β_2-adrenoceptors in normal and hypertrophic rat kidney, Biochim. Biophys. Acta 845 (1985) 463–468.
[34] M. Manteuffel-Cymborowska, Differential role of polyamines in hyperplasia and hypertrophy, Acta Biochim. Pol. 40 (1993) 383–388.
[35] K. Matsumoto, T. Nakamura, Hepatocyte growth factor (HGF) as a tissue organizer for organogenesis and regeneration, Biochem. Biophys. Res. Commun. 239 (1997) 639–644.
[36] T. Igawa, K. Matsumoto, S. Kanda, Y. Saito, T. Nakamura, Hepatocyte growth factor may function as a renotropic factor for regeneration in rats with acute renal injury, Am. J. Physiol. 265 (1993) F61–F69.
[37] M. Joannidis, K. Spokes, T. Nakamura, D. Faletto, L.G. Cantley, Regional expression of hepatocyte growth factor/c-*met* in experimental renal hypertrophy and hyperplasia, Am. J. Physiol. 267 (1994) F231–F236.
[38] Y. Liu, E.M. Tolbert, A.M. Sun, L.D. Dworkin, In vivo and in vitro evidence for increased expression of HGF receptor in kidney of diabetic rat, Am. J. Physiol. 271 (1996) F1202–F1210.
[39] I. Higaki, I. Matsui-Yuasa, M. Terakura, H. Kinoshita, S. Otani, Increase in ornithine decarboxylase activity caused by hepatocyte growth factor in primary cultured adult rat hepatocytes, Hepatology 17 (1993) 99–102.
[40] M.A. Desiderio, G. Pogliaghi, P. Dansi, Hepatocyte growth factor-induced expression of ornithine decarboxylase, c-*met*, and c-*myc* is differently affected by protein kinase inhibitors in human hepatoma cells HepG2, Exp. Cell Res. 242 (1998) 401–409.
[41] S.G. Reddy, S.M. McIlheran, B.J. Cochran, L.L. Worth, L.A. Bishop, P.J. Brown, V.P. Knutson, M.K. Haddox, Multisite phosphorylation of ornithine decarboxylase in transformed macrophages results in increased intracellular enzyme stability and catalytic efficiency, J. Biol. Chem. 271 (1996) 24945–24953.
[42] J.D. Veldhuis, T.S. Harrison, J.M. Hammond, β-2-Adrenergic stimulation of ornithine decarboxylase activity in porcine granulosa cells in vitro, Biochim. Biophys. Acta 627 (1980) 123–130.
[43] J.G. Copeland, D.F. Larson, W.R. Roeske, D.H. Russell, J.R. Womble, β_2-Adrenoceptors regulate induction of myocardial ornithine decarboxylase in mice in vivo, Br. J. Pharmacol. 75 (1982) 479–483.
[44] G. Morris, T.A. Slotkin, *Beta*-2 adrenergic control of ornithine decarboxylase activity in brain regions of the developing rat, J. Pharmacol. Exp. Ther. 233 (1985) 141–147.
[45] S. Colombatto, L. Fasulo, M.A. Grillo, Modification of ornithine decarboxylase activity by adrenergic stimulation in cultured chicken spleen cells, Int. J. Biochem. 21 (1989) 1197–1201.

[46] M. Juráni, M. Vaneková, P. Vyboh, D. Lamosová, Enhanced ornithine decarboxylase activity of chick muscle cells in culture by β-adrenergic agonists, Methods Find. Exp. Clin. Pharmacol. 18 (1996) 13–17.
[47] M. Esler, Renal catecholamine metabolism, Miner. Electrolyte Metab. 15 (1989) 16–23.
[48] P.C. Hubbard, I.W. Henderson, Renal dopamine and the tubular handling of sodium, J. Mol. Endocrinol. 14 (1995) 139–155.
[49] M.F. Lokhandwala, F. Amenta, Anatomical distribution and function of dopamine receptors in the kidney, FASEB J. 5 (1991) 3023–3030.
[50] A. Crozat, J.J. Palvimo, M. Julkunen, O.A. Jänne, Comparison of androgen regulation of ornithine decarboxylase and *S*-adenosylmethionine decarboxylase gene expression in rodent kidney and accessory sex organs, Endocrinology 130 (1992) 1131–1144.
[51] N. Koibuchi, S. Matsuzaki, M. Sakai, H. Ohtake, S. Yamaoka, Heterogenous expression of ornithine decarboxylase gene in the proximal tubule of the mouse kidney following testosterone treatment, Histochemistry 100 (1993) 325–330.
[52] M.A. Desiderio, G. Lugaro, D. Galasso, M.P. Colombo, Effect of adrenergic and Ca^{2+} antagonists on increased ornithine decarboxylase expression in regenerating rat liver, Biochem. Pharmacol. 40 (1990) 1605–1613.
[53] S.K. Mani, J.M.C. Allen, J.H. Clark, J.D. Blaustein, B.W. O'Malley, Convergent pathways for steroid hormone- and neurotransmitter-induced rat sexual behavior, Science 265 (1994) 1246–1249.